REMARKS

Formal Matters

Claims 58-59 and 61-65 and 67 are pending after entry of the amendments set forth herein.

Claims 58-66 were examined and were rejected.

Claims 61- 65 are amended and claim 67 is new. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claim 64 and 65 and new claim 67 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: figure 2 and page 28, lines 7-10. Support for the amendment to Claim 61 maybe found on page 4, lines 15-16. Accordingly, no new matter is added by these amendments and their entry is respectfully requested.

Please replace claims 58-66 with the claim set provided above.

Claims 60 and 66 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejection Under §112, ¶1 – Written Description

Claims 58-66 were rejected on the grounds that the specification does not describe the subject matter of these claims so as to reasonably convey to the skilled artisan that the inventors had possession of the claimed invention at the time of filing. This rejection is respectfully traversed.

In support of this rejection, the Office Action states that "the specification does not disclose any polypeptide that specifically binds to TOSO or any antibody that binds or recognizes TOSO or has any function." (Office Action page 2). Applicants respectfully disagree.

The Written Description Guidelines indicate that such the subject claims are adequately described

The "Synopsis of Application of Written Description Guidelines" (hereafter "Synopsis"; posted

on the USPTO world wide website on March 1, 2000), to which Examiners of the USPTO must adhere, describes an example (Example 16) similar to that of the Applicants.

The specification of this example discloses a purified 55kDa polypeptide and contemplates but does not teach an antibody that specifically binds to this polypeptide. In this example the claim "An isolated antibody capable of binding to antigen X" is made and even without a working example. The guidelines state that "The disclosure meets the requirement under 35 USC 112 first paragraph as providing an adequate written description of the claimed invention."

In the instant case, the specification describes Toso protein in detail – including its amino acid sequence (see Fig. 2a and SEQ ID NO:2). Isolation of Toso and its structural and functional characterization is also described in detail (see, generally, Examples 1-5, pages 41-50). As such the specification provides a purified antigen (e.g. Toso). The specification further provides a description of anti-Toso antibodies on page 12, lines 15-25 page 13, lines 1-7 and page 28, lines 17-28 of the specification.

When examined using the guidance presented by these Guidelines, the subject matter of the instant claims, particularly those that claim antibody compositions such as claims 59, 61-65 and 67, is adequately described in the specification.

In addition to antibodies, the application as filed also describes proteins that are associated on the cell surface with Toso in a manner such that these proteins are close enough to Toso to be cross-linked by the reagent BS3 (see specification, page 41, lines 22-28). As illustrated in the attached product description from the manufacturer (Pierce Biotechnology, Rockford, IL), BS3 is a bivalent cross-linking reagent having a spacer arm of 11.4 Angstroms. Thus proteins cross-linked to Toso by BS3 co-localize on the cell surface at a distance of 11.4 Angstroms (or less) from Toso. This close association strongly suggests that the protein is bound to Toso.

The application described such a Toso-associated protein. This protein, which is about 90 kDa, cross-linked to Toso after treatment with BS3, and was isolated as a cross-linked complex with Toso (specification, page 41, lines 22-28; page 42, lines 1-11and Fig. 10). This observation, coupled with the role of Toso in signal transduction in modulation of apoptosis suggests that the 90 kDa is an interacting partner of Toso, and binds Toso.

The Office Action further states that, in the context of determining whether the written description requirement is met for genus claims, "the specification does not describe structure of any

TOSO binding protein or any TOSO binding antibody." (Office Action, page 2). The Office Action further states that "no identifying characteristics have been described for any antibody. . . . While the claims describe 90% . . . sequence identity of the TOSO protein, no description is provided as to what characteristics the antibodies would have. . . . in the absence of description of their structure, an artisan would not know what was the structure of the claimed polypeptide or antibodies." (Office Action, page 3). Applicants respectfully disagree.

As noted above, the structure and function of Toso protein is provided in great detail in the application, and the function of Toso protein correlated with its structure. In addition to providing the amino acid sequence of Fig. 2a, the specification discloses that Toso is a type I integral membrane protein having extracellular, transmembrane, and cytoplasmic domains (see, e.g., page 32, line 18 to page 33, line 11). This structural analysis based on amino acid sequence was confirmed through deletion mutant analysis (see Example 3, page 39, line 3 to page 41, line 21). The function of Toso in inhibiting Fas-mediated apoptosis is also described in the specification (see, e.g., Example 2, page 35, line 3 to page 39, line 2).

In view of this vast amount of information regarding the structure and function relationship of Toso, the ordinarily skilled artisan would readily understand what regions of Toso could vary relative to SEQ ID NO:2. In addition, applicants are given guidance as to the types of variations there can be between Toso proteins (see, e.g., page 15, lines 21 to page 18, line 7).

Furthermore, the skilled artisan does not need to know the structure of an antibody that specifically binds a polypeptide of interest in order to recognize that the antibody is described. As noted above, antibody production is regarded as being routine in the art -- even where it may take a considerable amount of experimentation to obtain the antibody. The general structure of antibodies produced by immunization is known (i.e., a bivalent molecule having two heavy chains and two light chains). Furthermore, the structure of antigen-binding regions of antibodies is known (e.g., Fabs, and the like), as is the structure of single chain antibodies. In this case, a description of an antibody in terms of the antigen it binds is sufficient to describe the antibody.

In view of the remarks set out above, applicants respectfully request withdrawal of this rejection.

Rejections Under §112, ¶1 – Enablement

Claims 58-60, 64 and 65

Claims 58-60, 64 and 65 were rejected on the grounds that the specification, while being enabling for an antibody that binds to the TOSO protein of SEQ ID NO:2 or an antibody directed against the extracellular domain or cytoplasmic domains of SEQ ID NO:2, does not reasonably provide enablement for any protein that binds TOSO of SEQ ID NO:2 or to a TOSO protein that has 90% sequence identity to SEQ ID NO:2. This rejection is respectfully traversed.

The Applicants respectfully submit that claims 64, 65, 67 and 68 are directed to an antibody that binds to the TOSO protein of SEQ ID NO:2 or an antibody directed against the extracellular domain or cytoplasmic domains of SEQ ID NO:2. Since the Examiner has stated in the Office Action that an antibody that binds to the TOSO protein of SEQ ID NO:2 or an antibody directed against the extracellular domain or cytoplasmic domains of SEQ ID NO:2 is enabled, the rejection should be considered moot, and this rejection of claim 64, 65, 67 and 68 be withdrawn without any further discussion.

With respect to the other claims, in addition to antibodies, the specification describes the isolation of at least one protein that binds Toso protein, which protein was identified using the cross-linking reagent BS3 (see specification, page 41, lines 22-28). As illustrated in the attached product description from the manufacturer (Pierce Biotechnology, Rockford, IL), BS3 is a bivalent cross-linking reagent having a spacer arm of 11.4 Angstroms. Thus proteins cross-linked to Toso by BS3 co-localize on the cell surface at a distance of 11.4 Angstroms (or less) from Toso. This close association strongly suggests that the protein is bound to Toso.

In view of the above, applicants respectfully request withdrawal of this rejection.

Claims 61-63 and 66

Claims 61-63 and 66 were rejected on the grounds that the specification does not provide an enabling description of the subject matter of these claims. Specifically, the Office Action states that the specification "does not provide sufficient guidance as to what would be considered a TOSO protein, how would an artisan have made a polypeptide that binds to TOSO protein and used it or would have produced and used an anti-TOSO antibody for the intended utility.

Claim 66 is cancelled, and so the rejection, with respect to this claim, is moot.

Claims 61-63 are directed to antibodies that modulate the biological function of Toso in apoptosis.

As discussed above, the structure and biological function of Toso protein is provided in great detail in the application. In addition to providing the amino acid sequence of Fig. 2a, the specification discloses that Toso is a type I integral membrane protein having extracellular, transmembrane, and cytoplasmic domains (see, e.g., page 32, line 18 to page 33, line 11). This structural analysis based on amino acid sequence was confirmed through deletion mutant analysis (see Example 3, page 39, line 3 to page 41, line 21). The function of Toso in inhibiting Fas-mediated apoptosis is also described in the specification (see, e.g., Example 2, page 35, line 3 to page 39, line 2).

In view of this vast amount of information regarding the structure and function relationship of Toso, the ordinarily skilled artisan would readily understand what regions of Toso could vary relative to SEQ ID NO:2. In addition, applicants are given guidance as to the types of variations there can be between Toso proteins (see, e.g., page 15, lines 21 to page 18, line 7).

As such, the applicants have provided TOSO proteins, and experimentally established beyond doubt function of TOSO in apoptosis.

Antibodies are produced by one of skill in the art using very routine methodologies (for example, see Harlow et al,. *Antibodies: A Laboratory Manual*, First Edition (1988) Cold Spring Harbor, N.Y.). In fact, the "Synopsis of Application of Written Description Guidelines" supports this assertion. With respect to antibodies, the Synopsis states, on page 60, that "This is a mature technology where the level is high and advanced".

Since antibody production is a mature art, one of skill in the art needs little guidance in making an anti-TOSO antibody. Accordingly, the Applicants respectfully submit that anti-TOSO antibodies are enabled.

With respect to the intended utility of the antibodies in modulating the biological function of Toso in apoptosis, one of skill in the art would merely have to screen the antibodies for an ability TOSO's function in apoptosis. Methods for determining TOSO's function in apoptosis are described in great detail in Example 2, on pages 35-39, Example 3, on pages 39-42, Example 4, on pages 42-48 and, Example 5, on pages 48-50 of the specification.

As such, one of skill in the art, in order to assay antibodies that disrupt TOSO's function in apoptosis, would merely have to screen the antibodies using any one of these assays. Since TOSO is a transmembrane protein that that is involved in several protein-protein interactions, both intracellular and

extracellular (see figure 10), antibodies with TOSO-modulatory activity would be identified in these assays.

The Courts[1] and the MPEP §2164.01 clearly teach that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In fact, as the courts explained *In re Wands*[2]:

> [A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

The Applicants respectfully submit that the antibody screening arts typically engage in some routine experimentation. Since the function of TOSO in apoptosis has been established without any doubt, and several detailed protocols for assays for determining TOSO function in apoptosis are provided in the specification, the Applicants respectfully submit that one of skill in the art would be able to make and use the compositions encompassed by claims 61-63 without undue experimentation.

In view of the above, the Examiner is respectfully requested to withdraw this rejection.

Rejection Under §102(e)

Claims 58-60 and 64-65 were rejection as being anticipated by Wu et al. (US Pat. No. 6,111,515), which has an effective filing date of August 25, 1997. This rejection is respectfully traversed.

Applicants note that the August 25, 1997 filing date is that of a provisional application to which the application that led to the Wu et al. patent claims priority. The content of that provisional application and the content of the application that led to the Wu et al. patent (USSN 08961,564, filed October 30, 1997) may differ substantially. As such, the Applicants respectfully question whether Wu et

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[1] *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

[2] *In re Wands* 8 USPQ 2d at 1404

al.'s provisional application disclosed proteins that specifically bind Toso, including anti-Toso antibodies.

Nevertheless, the Applicants can establish that the claimed subject matter was reduced to practice by the inventors prior to Wu et al.'s August 25, 1997 priority date. This discussion should not be taken as any concession that Wu et al.'s provisional application disclosed proteins that specifically bind Toso, including anti-Toso antibodies.

As set out in 37 C.F.R. §1.131:

> (a) When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§1.42, 1.43, or 1.47, ***may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference*** or activity on which the rejection is based. . . .
>
> (b) ***The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference***, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application. . . .

(emphasis added)

As such, a 102(e) rejection may be withdrawn if the Applicants can establish, by means of a declaration and a showing of facts, that the claimed subject matter was reduced to practice prior to the effective filing date of the cited reference.

In order to establish that the claimed invention was reduced to practice prior to the August 25, 1997 priority date of Wu et al., applicants submit herewith the Declaration of Yasumichi Hitoshi Under 37 C.F.R. §1.131. This declaration provides a showing a facts that the inventors reduced to practice the claimed invention prior to the August 25, 1997 effective date of the reference in that the inventors had produced antibodies that specifically bind to the TOSO protein.

Since the Applicants have provided a declaration and facts that show a reduction to practice prior to the August 25, 1997 priority date of Wu et al, the rejection may be withdrawn. Withdrawal of this rejection is therefore respectfully requested.

CONCLUSION

In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

If the Examiner finds that a Telephone Conference would expedite prosecution of this application, he is invited to contact the undersigned (650) 327-3400.

In the event that the transmittal letter is separated from this document and the Patent Office determines that extensions or other relief is required and/or fees are due applicants, the Applicant petitions for any required relief, including extensions of time, and authorize the Commissioner to charge our Deposit Account No. 50-0815, Order Number RIGL-001, for any fees due in connection with the filing of this document. The Patent Office is not authorized to charge issue fees to our Deposit Account.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 6, 2003

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Enclosures: Copy of Declaration of Yasumichi Hitoshi, M.D., Ph.D with Exhibits A and B